

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Venlablue XL 150mg Prolonged Release Capsules, Hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains: Venlafaxine hydrochloride, corresponding to 150 mg Venlafaxine.

Excipients with known effect: allura red (E129) 0.198 mg, brilliant blue (E133) 0.009 mg and sunset yellow (E110) 0.396 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard

Dark orange / dark orange opaque, size '0' hard gelatin capsules having thick and thin radial circular band on the body in white ink and thick and thin radial circular band on the cap in white ink. The capsule is filled with 12 white to off-white, round, biconvex, film coated mini tablets of 12.5 mg each

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes.

For prevention of recurrence of major depressive episodes

Treatment of social anxiety disorder

4.2 Posology and method of administration

Posology

Paediatric population

Venlafaxine Bluefish is not recommended for use in children and adolescents under the age of 18 years.

Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy and do not support the use of venlafaxine in these patients (see sections 4.4 and 4.8).

The safety and efficacy of Venlablue XL for other indications in children and adolescents under the age of 18 have not been established.

Major depressive episodes

The recommended starting dose for prolonged-release venlafaxine is 75 mg given once daily. Patients not responding to the initial 75 mg/day dose may benefit from dose increases up to a maximum dose of 375 mg/day. Dosage increases can be made at intervals of 2 weeks or more. If clinically warranted due to symptom severity, dose increases can be made at more frequent intervals, but not less than 4 days.

Because of the risk of dose-related adverse effects, dose increments should be made only after a clinical evaluation (see section 4.4). The lowest effective dose should be maintained.

Patients should be treated for a sufficient period of time, usually several months or longer. Treatment should be reassessed regularly on a case-by-case basis. Longer-term treatment may also be appropriate for prevention of recurrence of major

depressive episodes (MDE). In most of the cases, the recommended dose in prevention of recurrence of MDE is the same as the one used during the current episode.

Antidepressive medicinal products should continue for at least six months following remission.

Social anxiety disorder

The recommended dose for prolonged-release venlafaxine is 75 mg given once daily. There is no evidence that higher doses confer any additional benefit.

However, in individual patients not responding to the initial 75 mg/day, increases up to a maximum dose of 225 mg/day may be considered. Dosage increases can be made at intervals of 2 weeks or more.

Because of the risk of dose-related adverse effects, dose increments should be made only after a clinical evaluation (see section 4.4). The lowest effective dose should be maintained.

Patients should be treated for a sufficient period of time, usually several months or longer. Treatment should be reassessed regularly, on a case-by-case basis.

Use in elderly patients

No specific dose adjustments of venlafaxine are considered necessary based on patient age alone. However, caution should be exercised in treating the elderly (e.g. due to the possibility of renal impairment, the potential for changes in neurotransmitter sensitivity and affinity occurring with aging). The lowest effective dose should always be used and patients should be carefully monitored when an increase in the dose is required.

Patients with hepatic impairment

In patients with mild and moderate hepatic impairment, in general a 50% dose reduction should be considered. However, due to inter-individual variability in clearance, individualisation of dosage may be desirable.

There are limited data in patients with severe hepatic impairment. Caution is advised, and a dose reduction by more than 50% should be considered. The potential benefit should be weighed against the risk in the treatment of patients with severe hepatic impairment.

Patients with renal impairment

Although no change in dosage is necessary for patients with glomerular filtration rate (GFR) between 30-70 ml/minute, caution is advised. For patients that require haemodialysis and in patients with severe renal impairment (GFR < 30 ml/min), the dose should be reduced by 50%. Because of inter-individual variability in clearance in these patients, individualisation of dosage may be desirable.

Withdrawal symptoms seen on discontinuation of venlafaxine

Abrupt discontinuation should be avoided. When stopping treatment with venlafaxine, the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

Method of administration

For oral use.

It is recommended that Venlablue XLprolonged-release capsules be taken with food, at approximately the same time each day. Capsules must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

Patients treated with venlafaxine immediate-release tablets may be switched to venlafaxine prolonged-release capsules at the nearest equivalent daily dosage. For example, venlafaxine immediate-release tablets 37.5 mg twice daily may be switched to venlafaxine prolonged-release capsules 75 mg once daily. Individual dosage adjustments may be necessary.

Venlablue XL prolonged-release capsules contain spheroids, which release the active substance slowly into the digestive tract. The insoluble portion of these spheroids is eliminated and may be seen in faeces.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia.

Venlafaxine must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI.

Venlafaxine must be discontinued for at least 7 days before starting treatment with an irreversible MAOI (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Paediatric population

Venlablue XL should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Overdose

Patients should be advised not to use alcohol, considering its CNS-effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interactions with venlafaxine including CNS depressant effects (section 4.5). Overdose with venlafaxine has been reported predominantly in combination with alcohol and/or other medicinal products, including cases with fatal outcome (section 4.9).

Prescriptions for venlafaxine should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose (see 4.9).

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which venlafaxine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult

patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Serotonin syndrome

As with other serotonergic agents, the development of a potentially life-threatening serotonin-syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions, may occur with venlafaxine treatment, particularly with concomitant use of other serotonergic agents (including SSRIs, SNRIs and triptans), with agents that impair metabolism of serotonin such as MAO-inhibitors (e.g. methylene blue), with antipsychotics and other dopamine antagonists (see sections 4.3 and 4.5) and with opioids.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

Serotonin syndrome in its most severe form, can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs and mental status changes.

If concomitant treatment with venlafaxine and other agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended.

Narrow-angle glaucoma

Mydriasis may occur in association with venlafaxine. It is recommended that patients with raised intraocular pressure or patients at risk for acute narrow-angle glaucoma (angle-closure glaucoma) be closely monitored.

Blood pressure

Dose-related increases in blood pressure have been commonly reported with venlafaxine. In some cases, severely elevated blood pressure requiring immediate treatment has been reported in post-marketing experience. All patients should be carefully screened for high blood pressure and pre-existing hypertension should be controlled before initiation of treatment. Blood pressure should be reviewed periodically, after initiation of treatment and after dose increases. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure, e.g., those with impaired cardiac function.

Heart rate

Increases in heart rate can occur, particularly with higher doses. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate.

Cardiac disease and risk of arrhythmia

Venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients.

In post-marketing experience, fatal cardiac arrhythmias have been reported with the use of venlafaxine, especially in overdose. The balance of risks and benefits should be considered before prescribing venlafaxine to patients at high risk of serious cardiac arrhythmia.

Convulsions

Convulsions may occur with venlafaxine therapy. As with all antidepressants, venlafaxine should be introduced with caution in patients with a history of convulsions, and concerned patients should be closely monitored. Treatment should be discontinued in any patient who develops seizures.

Hyponatraemia

Cases of hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur with venlafaxine. This has most frequently been reported in volume-depleted or dehydrated patients. Elderly patients, patients taking diuretics, and patients who are otherwise volume-depleted may be at greater risk for this event.

Abnormal bleeding

Medicinal products that inhibit serotonin uptake may lead to reduced platelet function. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to gastrointestinal and life-threatening haemorrhages. The risk of haemorrhage, may be increased in patients taking venlafaxine. SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8). As with other serotonin-reuptake inhibitors, venlafaxine should be used cautiously in patients predisposed to bleeding, including patients on anticoagulants and platelet inhibitors.

Serum cholesterol

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled clinical trials. Measurement of serum cholesterol levels should be considered during long-term treatment.

Co-administration with weight loss agents

The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Co-administration of venlafaxine and weight loss agents is not recommended. Venlafaxine is not indicated for weight loss alone or in combination with other products.

Mania/hypomania

Mania/hypomania may occur in a small proportion of patients with mood disorders who have received antidepressants, including venlafaxine. As with other antidepressants, venlafaxine should be used cautiously in patients with a history or family history of bipolar disorder.

Aggression

Aggression may occur in a small number of patients who have received antidepressants, including venlafaxine. This has been reported under initiation, dose changes and discontinuation of treatment.

As with other antidepressants, venlafaxine should be used cautiously in patients with a history of aggression.

Discontinuation of treatment

Withdrawal symptoms, when treatment is discontinued, are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse events seen on treatment discontinuation (tapering and post-tapering) occurred in approximately 31% of patients treated with venlafaxine and 17% of patients taking placebo.

The risk of withdrawal symptoms may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances(including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that venlafaxine should be

gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see section 4.2).

Akathisia/psychomotor restlessness

The use of venlafaxine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Dry mouth

Dry mouth is reported in 10% of patients treated with venlafaxine. This may increase the risk of caries, and patients should be advised upon the importance of dental hygiene.

Diabetes

In patients with diabetes, treatment with an SSRI or venlafaxine may alter glycaemic control. Insulin and/or oral antidiabetic dosage may need to be adjusted.

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking venlafaxine. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of venlafaxine therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish venlafaxine from PCP and amphetamine.

The colouring agents allura red, sunset yellow and brilliant blue may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine Oxidase Inhibitors (MAOI)

Irreversible non-selective MAOIs

Venlafaxine must not be used in combination with irreversible non-selective MAOIs. Venlafaxine must not be initiated for at least 14 days after discontinuation of treatment with an irreversible nonselective MAOI. Venlafaxine must be discontinued for at least 7 days before starting treatment with an irreversible non-selective MAOI (see sections 4.3 and 4.4).

Reversible, selective MAO-A inhibitor (moclobemide)

Due to the risk of serotonin syndrome, the combination of venlafaxine with a reversible and selective MAOI, such as moclobemide, is not recommended. Following treatment with a reversible MAO-inhibitor, a shorter withdrawal period than 14 days may be used before initiation of venlafaxine treatment. It is recommended that venlafaxine should be discontinued for at least 7 days before starting treatment with a reversible MAOI (see section 4.4).

Reversible, non-selective MAOI (linezolid)

The antibiotic linezolid is a weak reversible and non-selective MAOI and should not be given to patients treated with venlafaxine (see section 4.4).

Severe adverse reactions have been reported in patients who have recently been discontinued from an MAOI and started on venlafaxine, or have recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death.

Serotonin syndrome

As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with venlafaxine treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, lithium, sibutramine, tramadol, buprenorphine or St. John's Wort [*Hypericum perforatum*]),, with medicinal agents that impair metabolism of serotonin (such as MAOIs e.g. methylene blue), or with serotonin precursors (such as tryptophan supplements)

If concomitant treatment with venlafaxine and an SSRI, an SNRI, a serotonin receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended (see section 4.4).

CNS-active substances

The risk of using venlafaxine in combination with other CNS-active substances has not been systematically evaluated. Consequently, caution is advised when venlafaxine is taken in combination with other CNS-active substances.

Ethanol

Patients should be advised not to use alcohol, considering its CNS-effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interactions with venlafaxine including CNS depressant effects.

Effect of venlafaxine on other medicinal products

Drugs Metabolized by Cytochrome P450 Isoenzymes

In vivo studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP3A4 (alprazolam and carbamazepine), CYP1A2 (caffeine), and CYP2C9 (tolbutamide) or CYP2C19 (diazepam) in vivo.

Effect of other medicinal products on venlafaxine

Ketoconazole (CYP3A4 inhibitor)

A pharmacokinetic study with ketoconazole in CYP2D6 extensive (EM) and poor metabolisers (PM) resulted in higher AUC of venlafaxine (70% and 21% in CYP2D6 PM and EM subjects, respectively) and O-desmethylvenlafaxine (33% and 23% in CYP2D6 PM and EM subjects, respectively) following administration of ketoconazole. Concomitant use of CYP3A4 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, voriconazole, posaconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, telithromycin) and venlafaxine may increase levels of venlafaxine and O-desmethylvenlafaxine. Therefore, caution is advised if a patient's therapy includes a CYP3A4 inhibitor and venlafaxine concomitantly.

Effect of venlafaxine on other medicinal products

Lithium

Serotonin syndrome may occur with the concomitant use of venlafaxine and lithium (see Serotonin syndrome).

Diazepam

Venlafaxine has no effects on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam. Diazepam does not appear to affect the pharmacokinetics of either venlafaxine or O-desmethylvenlafaxine. It is unknown whether a pharmacokinetic and/or pharmacodynamic interaction with other benzodiazepines exists.

Imipramine

Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. There was a dose-dependent increase of 2-OH-desipramine AUC by 2.5 to 4.5-fold when venlafaxine 75 mg to 150 mg daily was administered. Imipramine did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown. Caution should be exercised with co-administration of venlafaxine and imipramine.

Haloperidol

A pharmacokinetic study with haloperidol has shown a 42% decrease in total oral clearance, a 70% increase in AUC, an 88% increase in C_{max} , but no change in half-life for haloperidol. This should be taken into account in patients treated with haloperidol and venlafaxine concomitantly. The clinical significance of this interaction is unknown.

Risperidone

Venlafaxine increased the risperidone AUC by 50%, but did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). The clinical significance of this interaction is unknown.

Metoprolol

Concomitant administration of venlafaxine and metoprolol to healthy volunteers in a pharmacokinetic interaction study for both medicinal products resulted in an increase of plasma concentrations of metoprolol by approximately 30-40% without altering the plasma concentrations of its active metabolite, α -hydroxymetoprolol. The clinical relevance of this finding in hypertensive patients is unknown. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, O-desmethylvenlafaxine. Caution should be exercised with co-administration of venlafaxine and metoprolol.

Indinavir

A pharmacokinetic study with indinavir has shown a 28% decrease in AUC and a 36% decrease in C_{max} for indinavir. Indinavir did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown.

Drugs Metabolized by Cytochrome P450 Isoenzymes

In vivo studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP3A4 (alprazolam and carbamazepine), CYP1A2 (caffeine), and CYP2C9 (tolbutamide) or CYP2C19 (diazepam) in vivo.

Oral contraceptives

In post-marketing experience unintended pregnancies have been reported in subjects taking oral contraceptives while on venlafaxine. There is no clear evidence these pregnancies were a result of drug interaction with venlafaxine. No interaction study with hormonal contraceptives has been performed.

4.6 Fertility, pregnancy and lactation*Pregnancy*

There are no adequate data from the use of venlafaxine in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Venlafaxine must only be administered to pregnant women if the expected benefits outweigh any possible risk.

As with other serotonin reuptake inhibitors (SSRIs/SNRIs), discontinuation symptoms may occur in the newborns if venlafaxine is used until or shortly before birth. Some newborns exposed to venlafaxine late in the third trimester have developed complications requiring tube-feeding, respiratory support or prolonged hospitalisation. Such complications can arise immediately upon delivery.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated an association of PPHN to SNRI treatment, this potential risk cannot be ruled out with venlafaxine taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

The following symptoms may be observed in neonates if the mother has used an SSRI/SNRI late in pregnancy: irritability, tremor, hypotonia, persistent crying, and difficulty in sucking or in sleeping.

These symptoms may be due to either serotonergic effects or exposure symptoms. In the majority of cases, these complications are observed immediately or within 24 hours after partus.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).

Breast-feeding

Venlafaxine and its active metabolite, O-desmethylvenlafaxine, are excreted in breast milk. There have been post-marketing reports of breast-fed infants who experienced crying, irritability, and abnormal sleep patterns. Symptoms consistent with

venlafaxine drug discontinuation have also been reported after stopping breast-feeding. A risk to the suckling child cannot be excluded. Therefore, a decision to continue/discontinue breast-feeding or to continue/discontinue therapy with Venlablue XL should be made, taking into account the benefit of breast-feeding to the child and the benefit of Venlablue XL therapy to the woman.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated an association of PPHN to SNRI treatment, this potential risk cannot be ruled out with Venlafaxine taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

4.7 Effects on ability to drive and use machines

Any psychoactive medicinal product may impair judgment, thinking, and motor skills. Therefore, any patient receiving venlafaxine should be cautioned about their ability to drive or operate hazardous machinery.

4.8 Undesirable effects

Paediatric population

In general, the adverse reaction profile of venlafaxine (in placebo-controlled clinical trials) in children and adolescents (ages 6 to 17) was similar to that seen for adults. As with adults, decreased appetite, weight loss, increased blood pressure, and increased serum cholesterol were observed (see section 4.4).

In paediatric clinical trials the adverse reaction suicidal ideation was observed. There were also increased reports of hostility and, especially in major depressive disorder, self-harm.

Particularly, the following adverse reactions were observed in paediatric patients: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis, and myalgia.

The most commonly (>1/10) reported adverse reactions in clinical studies were nausea, dry mouth, headache and sweating (including night sweats).

Adverse reactions are listed below by system organ class and frequency.

Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); not known (cannot be estimated from the available data).

Body system	Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders					Thrombocytopenia, Blood Disorder including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia
Immune system disorders					Anaphylactic reaction
Endocrine disorders					Syndrome of Inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders		Decreased appetite			Hyponatraemia
Psychiatric disorders		Confusional state, Depersonalization, Anorgasmia,	Hallucination, Derealization, Agitation, Orgasm abnormal	Mania	Suicidal ideation and suicidal behaviours*, Delirium, Aggression**

		Libido decreased, Nervousness, Insomnia, Abnormal dreams	(female), Apathy, Hypomania, Bruxism		
Nervous system disorder	Dizziness, Headache***	Somnolence, Tremor, Paraesthesia, Hypertonia	Akathisia/ Psychomotor restlessness, Syncope, Myoclonus, Coordination abnormal, Balance disorder, Dysgeusia	Convulsion	Neuroleptic Malignant Syndrome (NMS), Serotonergic syndrome, Extrapyramidal disorderincluding dystonia and dyskinaesia, Tardive dyskinaesia,
Eye disorders		Visual impairment, including vision blurred, Mydriasis, Accommodation disorder			Angle-closure glaucoma
Ear and labyrinth disorders		Tinnitus			Vertigo
Cardiac disorder		Palpitations	Tachycardia		Ventricular fibrillation, Ventricular tachycardia (including torsade de pointes)
Vascular disorders		Hypertension, Vasodilatation (mostly flush)	Orthostatic hypotension		Hypotension, Bleeding (mucous membrane bleeding)
Respiratory, thoracic and mediastinal disorder		Yawning	Dyspnoea		Pulmonary eosinophilia
Digestive Gastrointestinal disorders	Nausea, Dry mouth	Vomiting, Diarrhoea, Constipation	Gastrointestinal haemorrhage		Pancreatitis
Hepatobiliary disorders					Hepatitis, Liver function test abnormal
Skin and subcutaneous tissue disorders	Hyperhidrosis (including night sweats)		Angioedema, Photosensitivity reaction, Ecchymosis,Rash, Alopecia		Erythema multiforme, Toxic epidermal necrolysis, Stevens- Johnson syndrome, Pruritus, Urticaria
Musculoskeletal and connective tissue disorders					Rhabdomyolysis
Renal and urinary disorders		Dysuria (mostly urinary hesitation), Pollakiuria	Urinary retention	Urinary incontinence	
Reproductive system and breast disorder		Menstrual disorders associated with			postpartum haemorrhage****

		increased bleeding or irregular bleeding (e.g., menorrhagia, metrorrhagia) Ejaculation disorder, Erectile dysfunction			
General disorders and administration site conditions		Asthenia, Fatigue, Chills			
Investigations		Blood cholesterol increased	Weight increased, Weight decreased		Electrocardiogram QT prolonged, Bleeding time prolonged, Blood prolactin increased

*Cases of suicidal ideation and suicidal behaviours have been reported during venlafaxine therapy or early after treatment discontinuation (see section 4.4).

**See section 4.4

***In pooled clinical trials, the incidence of headache with venlafaxine and placebo were similar.

**** This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4, 4.6).

Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, vertigo, head ache and flu syndrome are the most commonly reported reactions. Generally, these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when venlafaxine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

HPRA Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

In post-marketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other medicinal products including cases with fatal outcome. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, convulsion, and vomiting. Other reported events include electrocardiographic changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, vertigo, and death. Severe poisoning symptoms may occur in adults after intake of approximately 3 grams of venlafaxine.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine treated patients have a higher burden of suicide risk factors than SSRI patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristics of venlafaxine-treated patients, is not clear.

Recommended treatment

Severe poisoning may require complex emergency treatment and monitoring. Therefore, in event of suspected overdose involving venlafaxine, prompt contact with [e.g. national poison information center, poisoning specialist, to be adapted nationally] is recommended.

General supportive and symptomatic measures are recommended; cardiac rhythm and vital signs must be monitored. When there is a risk of aspiration, induction of emesis is not recommended. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Administration of activated charcoal may also limit absorption of the active substance. Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants

ATC code: N06AX16

The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine (ODV), are inhibitors of serotonin and noradrenaline re-uptake. Venlafaxine also weakly inhibits dopamine uptake. Venlafaxine and its active metabolite reduce β -adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and ODV are very similar with respect to their overall action on neurotransmitter reuptake and receptor binding.

Venlafaxine has virtually no affinity for rat brain muscarinic, cholinergic, H_1 -histaminergic or α_1 -adrenergic receptors *in vitro*. Pharmacological activity at these receptors may be related to various side effects seen with other antidepressant medicinal products, such as anticholinergic, sedative and cardiovascular side effects. Venlafaxine does not possess monoamine oxidase (MAO) inhibitory activity.

In vitro studies revealed that venlafaxine has virtually no affinity for opiate or benzodiazepine sensitive receptors.

Major depressive episodes

The efficacy of venlafaxine immediate-release as a treatment for major depressive episodes was demonstrated in five randomised, double-blind, placebo-controlled, short-term trials ranging from 4 to 6 weeks duration, for doses up to 375 mg/day. The efficacy of venlafaxine prolonged-release as a treatment for major depressive episodes was established in two placebo-controlled, short-term studies for 8 and 12 weeks duration, which included a dose range of 75 to 225 mg/day.

In one longer-term study, adult outpatients who had responded during an 8-week open trial on venlafaxine prolonged-release (75, 150, or 225 mg) were randomised to continuation of their same venlafaxine prolonged-release dose or to placebo, for up to 26 weeks of observation for relapse.

In a second longer-term study, the efficacy of venlafaxine in prevention of recurrent depressive episodes for a 12-month period was established in a placebo-controlled double-blind clinical trial in adult outpatients with recurrent major depressive episodes who had responded to venlafaxine treatment (100 to 200 mg/day, on a b.i.d. schedule) on the last episode of depression.

Social anxiety disorder

The efficacy of venlafaxine prolonged-release capsules as a treatment for social anxiety disorder was established in four double-blind, parallel-group, 12-week, multi-center, placebo-controlled, flexible-dose studies and one double-blind, parallel-group, 6-month, placebo-controlled, fixed/flexible-dose study in adult outpatients. Patients received doses in a range of 75 to 225 mg/day. There was no evidence for any greater effectiveness of the 150 to 225 mg/day group compared to the 75 mg/day group in the 6-month study.

5.2 Pharmacokinetic properties

Venlafaxine is extensively metabolised, primarily to the active metabolite, O-desmethylvenlafaxine (ODV). Mean \pm SD plasma half-lives of venlafaxine and ODV are 5 ± 2 hours and 11 ± 2 hours, respectively. Steady-state concentrations of venlafaxine and ODV are attained within 3 days of oral multiple-dose therapy. Venlafaxine and ODV exhibit linear kinetics over the dose range of 75 mg to 450 mg/day.

Absorption

At least 92% of venlafaxine is absorbed following single oral doses of immediate-release venlafaxine. Absolute bioavailability is 40% to 45% due to presystemic metabolism. After immediate-release venlafaxine administration, the peak plasma concentrations of venlafaxine and ODV occur in 2 and 3 hours, respectively. Following the administration of venlafaxine prolonged-release capsules, peak plasma concentrations of venlafaxine and ODV are attained within 5.5 hours and 9 hours, respectively. When equal daily doses of venlafaxine are administered as either an immediate-release tablet or prolonged-release capsule, the prolonged-release capsule provides a slower rate of absorption, but the same extent of absorption compared with the immediate-release tablet. Food does not affect the bioavailability of venlafaxine and ODV.

Distribution

Venlafaxine and ODV are minimally bound at therapeutic concentrations to human plasma proteins (27% and 30%, respectively). The volume of distribution for venlafaxine at steady-state is 4.4 ± 1.6 L/kg following intravenous administration.

Biotransformation

Venlafaxine undergoes extensive hepatic metabolism. *In vitro* and *in vivo* studies indicate that venlafaxine is biotransformed to its major active metabolite, ODV, by CYP2D6. *In vitro* and *in vivo* studies indicate that venlafaxine is metabolised to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4. *In vitro* and *in vivo* studies indicate that venlafaxine is a weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2, CYP2C9, or CYP3A4.

Elimination

Venlafaxine and its metabolites are excreted primarily through the kidneys. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Mean \pm SD plasma steady-state clearances of venlafaxine and ODV are 1.3 ± 0.6 L/h/kg and 0.4 ± 0.2 L/h/kg, respectively.

Special populations

Age and gender

Subject age and gender do not significantly affect the pharmacokinetics of venlafaxine and ODV.

CYP2D6 extensive/poor metabolisers

Plasma concentrations of venlafaxine are higher in CYP2D6 poor metabolisers than extensive metabolisers. Because the total exposure (AUC) of venlafaxine and ODV is similar in poor and extensive metabolisers, there is no need for different venlafaxine dosing regimens for these two groups.

Patients with hepatic impairment

In Child-Pugh A (mildly hepatically impaired) and Child-Pugh B (moderately hepatically impaired) subjects, venlafaxine and ODV half-lives were prolonged compared to normal subjects. The oral clearance of both venlafaxine and ODV was reduced. A large degree of intersubject variability was noted. There are limited data in patients with severe hepatic impairment (see section 4.2).

Patients with renal impairment

In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance reduced by about 57% compared to normal subjects, while ODV elimination half-life was prolonged by about 142% and clearance reduced by about 56%. Dosage adjustment is necessary in patients with severe renal impairment and in patients that require haemodialysis (see section 4.2).

5.3 Preclinical safety data

Studies with venlafaxine in rats and mice revealed no evidence of carcinogenesis. Venlafaxine was not mutagenic in a wide range of *in vitro* and *in vivo* tests.

Animal studies regarding reproductive toxicity have found in rats a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation. The cause of these deaths is unknown. These effects occurred at 30 mg/kg/day, 4 times the human daily dose of 375 mg of venlafaxine (on an mg/kg basis). The no-effect dose for these findings was 1.3 times the human dose. The potential risk for humans is unknown.

Reduced fertility was observed in a study in which both male and female rats were exposed to ODV. This exposure was approximately 1 to 2 times that of a human dose of 375mg/day. The human relevance of this finding is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

microcrystalline cellulose
povidone
talc
silica, colloidal anhydrous
magnesium stearate

Tablet film coat:

ethyl cellulose
copovidone

Capsule:

allura red (E129)
sunset yellow FCF (E110)
brilliant blue FCF (E133)
titanium dioxide (E171)
gelatin

Printing Inks:

shellac
titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister packs of opaque, white PVC/Aclar film and aluminium foil; 10, 14, 28, 30, 50& 100 capsules

Blister packs of opaque, white PVC/PVdC film and aluminium foil; 10, 14, 28, 30, 50& 100 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bluefish Pharmaceuticals AB
P.O. Box 49013
100 28 Stockholm
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8 MARKETING AUTHORISATION NUMBER

PA1436/006/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th April 2010
Date of last renewal: 18th March 2015

10 DATE OF REVISION OF THE TEXT

July 2023